**Title: Retinal sensitivity changes associated with diabetic neuropathy in the absence of diabetic retinopathy.**

**Subtitle: Diabetic neuropathy and early retinal markers**

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**SYNOPSIS:**

In this study, we found a significant association of reduced retinal sensitivity, measured using microperimetry, in subjects who had diabetic neuropathy but no diabetic retinopathy. This suggests retinal function loss preceding vascular damage in subjects with peripheral diabetic neuropathy.

**ABSTRACT:**

**Purpose:** To explore any relationship between the markers of early retinal neuronal damage and peripheral diabetic neuropathy in subjects with no diabetic retinopathy (DR)

**Methods:** A cross-sectional study in which type 2 diabetic subjects (n=743) without DR were studied. Visual functions including visual acuity, contrast sensitivity, colour vision, retinal sensitivity using microperimeter and retinal thicknesses by spectral domain optical coherence tomography were measured. Vibration perception thresholds of greater than or equal to 20 µv, measured by sensitometer using a biothesiometer probe, were defined as having peripheral diabetic neuropathy. Statistical analyses were performed using independent t-test, multivariate logistic regression and Pearson’s correlation.

**Results:** Of 743 subjects who had no DR, 24.9% had diabetic neuropathy. Independent comparisons among subjects who had diabetic neuropathy compared to those who did not showed statistically significant retinal nerve fibre layer thinning (p = 0.01), reduced contrast sensitivity (p =0.0001), reduced retinal sensitivity (p = 0.03), impaired colour vision (p = 0.04) and reduced LogMAR visual acuity (p =0.0001). Multivariate analysis showed significant association between the mean retinal sensitivity (measured using a microperimeter) and diabetic neuropathy (adjusted odds ratio (95% CI): 0.76 (0.60-0.95), p = 0.01).

**Conclusion:** Significant association of neuro-retinal dysfunction with the presence of diabetic neuropathy was noted among subjects with no diabetic retinopathy.

Keywords: Type 2 diabetes, diabetic neuropathy, retinal sensitivity, biomarkers

**INTRODUCTION**

Diabetic microangiopathies are major contributors of morbidity among people with diabetes. The microangiopathies share common pathophysiological, metabolic and ischemic mechanisms that are triggered by hyperglycaemia.[1] It is therefore expected that various diabetic complications may co-exist. Epidemiological studies have shown associations between diabetic retinopathy (DR) and nephropathy in the same subjects.[2,3] However, these relationships have not been established conclusively.[4] It is possible that the different time periods for the severity of these two conditions to be established accounts for this.

Visual function loss in diabetes is well reported in the literature. It has been postulated that altered ocular blood flow and changes in foveal thickness may lead to reduced visual acuity and contrast sensitivity in subjects with diabetes. Diabetic eyes also show loss in colour vision possibly due to a disruption of neural retina as a consequence of hypoxic changes. Reductions in retinal nerve fibre layer thickness (measured using optical coherence tomography (OCT)), contrast sensitivity, retinal sensitivity, and multifocal Electroretinogram (mfERG) amplitudes suggest that retinal neuronal damage occurs before the onset of DR in diabetes.[5-11] In addition, diabetic neuropathy (DN) has also been significantly associated with neural changes such as RNFL thinning and decreased peripheral visual field sensitivity[12, 13], suggesting that neuronal damage may be more associated with DN rather than vasculopathy.[12]

There is limited literature on visual function and retinal structural changes which are indicative of early neuronal damage in subjects who have DN but no DR. The main aim of this study was to explore any possible associations between peripheral DN and early structural and functional changes in diabetic subjects who have no DR.

**MATERIALS AND METHODS**

Subjects were recruited from the Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study II (SN-DREAMS II) which was a follow-up study of SN-DREAMS I conducted between 2007 and 2010.[14] Data were collected on 743 subjects with type 2 diabetes. A signed informed consent was obtained from all the subjects. The study followed the declarations of Helsinki and was approved by the institutional review board and ethics committee.

All subjects underwent complete ophthalmic evaluation that included best corrected visual acuity (BCVA), slit-lamp examination and indirect ophthalmoscopy and retinal photographs using 45° four-field stereoscopic digital photography. The presence or absence of DR was defined using the modified Klein classification.[15] Subjects who showed evidence of any DR on additional 30° seven-field stereo digital pairs were excluded. All photographs were graded by two independent observers; the grading agreement was high (k = 0.83).[16]

Subjects with congenital colour deficiencies, history of any ophthalmological disease, significant cataract (more than N2 C1 P1) and any chronic disease not associated with diabetes that could affect the visual system were excluded, as were subjects who had received any laser photocoagulation therapy. Subjects with any other ocular disease including age related macular degeneration, glaucoma or optic nerve diseases were also excluded. Subjects displaying poor understanding and co-operation of the functional tests were also excluded.

**Visual Function tests:**

Monocular distance visual acuity was measured using the modified ETDRS chart (Light House Low Vision Products, New York, NY, USA). Objective streak retinoscopy was performed followed by detailed subjective refraction. Monocular contrast sensitivity was measured using the Pelli-Robson chart at a 1metre distance. All subjects were optimally corrected for the viewing distance. Contrast sensitivity data was collected from 613 literate subjects.

Monocular colour discrimination was performed using a Fransworth-Munsell 100 Hue test on 245 subjects. Colour discrimination was reported by the total error scores as suggested by the manufacturers. A video clip of the colour vision test demonstrated how the test worked. Subjects who could not understand or perform the test were excluded. Subjects whose monocular BCVA was worse than 0.3 logMAR and those who had cataracts were also excluded from testing.

Retinal sensitivity was measured on dilated eyes using the MP-1 microperimeter (Nidek Technologies, Padova, Italy). The mean retinal sensitivity in the central 20°area (over a grid of 76 stimuli) using a Goldmann 3mm stimuli was measured with a 4-2 double stair case strategy. The background intensity was 4 apostilbs. The stimuli were presented one at a time and the subject was asked to respond if they could see it by pressing a hand-held button while concentrating on the central fixation target. The data was collected from 245 subjects. Subjects who had a BCVA worse than 6/60 (n=24), significant media opacity (n=163), pupil size less than 4mm (n=75), unable to understand and perform MP-1 (n=236) were excluded from the microperimetry testing.

**Structural assessment:**

Retinal layer thickness was measured using Spectral Domain OCT (Copernicus, Optopol, Poland) in 605 subjects in both eyes. Dilated OCT measurements were obtained using the macular Asterisk scan and 3D scan protocols. A retinal map was acquired using the three-dimensional scan protocol with 50 B‑scans and 1000 A‑scans per B‑scan, centered on the subject’s ﬁxation point. Three-dimensional scan gave the retinal thicknesses at the central 1mm, inner 3mm and outer 6mm macula rings from the temporal, superior, inferior, and nasal subfield thicknesses quadrants. An average thickness from these 9 quadrants was taken as mean retinal thickness. Using the computer-based caliper measurement tool in the OCT system, the central foveal thickness was measured as the distance between the vitreo-retinal interface and the inner edge of the retinal pigment epithelium (RPE). The photoreceptor layer thickness was measured as the distance between the external limiting membrane (ELM), and the inner edge of the RPE. Automated macular RNFL and RPE thickness were also obtained using inbuilt topographic mapping software.[9] We could not analyze the scans in 138 subjects who had media haze.

**Diabetic neuropathy assessment:**

A single investigator measured vibration perception thresholds (VPT) using a sensitometer (Dhansai Laboratory, India) in all subjects. A biothesiometer probe was placed perpendicular to the foot at two anatomical locations - sole and medial malleolus in both right and left legs. A measurement was recorded when the subject felt the first vibration sensation of the sensitometer. An average of four readings was obtained for the two anatomical locations of both legs. DN was considered to be present if the average VPT was greater than or equal to 20 microvolts.[16]

**Statistical analysis:**

Statistical analyses were performed using the SPSS software for windows, version 17.0 (SPSS Inc., Chicago, IL, USA). Tests for normality were performed on all continuous data. Kolmogrov Smirnov and Shapiro Wilk tests showed that data were not normally distributed (p<0.05). In order to assume normality, the data were log transformed after which parametric tests were performed. Raw data are presented as the mean and standard deviations in Tables 1 and 2. The data were divided into two groups and the results have been described for those with DN (n= 185) and those without DN (n=558). Structural OCT and visual functions data from the right eye of all the subjects were subjected to statistical analysis. Independent t-test was performed to examine structural and functional variables in each group; variables that were shown to be significant were then fed into the multiple logistic regression analysis. Unadjusted and adjusted odd’s ratios were obtained for the significant variables. Parsimonious regression identified statistically significant (p<0.05) risk factors. Pearson’s correlations were performed to assess the correlations between the continuous variables of DN and retinal sensitivity in subjects with no DR.

**RESULTS**

Table 1 shows the demographic features of the study sample. Of the 743 subjects who had no DR, 25% (n=185) had DN. Subjects with DN (mean VPT: 14.52 ± 2.7 microvolts) were significantly older and had significantly longer duration of diabetes and increased systolic blood pressure (BP) compared to the no-DN group (mean VPT 27 ± 6.8 microvolts).

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| **Table 1: Demographic and systemic characteristics of the study sample** |
|   |   |   |   |
| Variables | Cohort without DNn(%)= 558(75.1) |  Cohort with DN n(%)=185(24.9) |   |
| mean ± SD | mean ± SD | *p* |
| Age(years) | 56.92 ± 8.8 | 63.95 ± 9.3 | 0.0001\* |
| Gender (male:female)  | 291:267 | 87:98 | 0.22^ |
| Duration of DM (years)  | 6.96 ± 4.6 | 9.96 ± 6.4 | 0.0001\* |
| Systolic BP (mm Hg) | 131.12 ±17.7 | 135.57±18.5 | 0.004\* |
| Diastolic BP (mm Hg) | 78.18±9.3 | 77.76±9.4 | 0.59 |
| HbA1c (%) | 7.18±1.6 | 7±1.6 | 0.24 |
| Albuminuria (mg/g) | 29.5±50.5 | 33.93±53.9 | 0.22 |
| Serum trigycerides (mg/dL) | 121.2±80.9 | 110.84±63.4 | 0.1 |
| Serum HDL (mg/dL) | 38.3±11.8 | 39.26±11 | 0.34 |
| Total cholesterol (mg/dL) | 167.85±40.67 | 172.14±39 | 0.21 |
| BMI (Kg/m2) | 64.43±10.45 | 64.34±11.53 | 0.93 |
| \* - p < 0.05, Independent t test, ^ - Chi square test, DN – Diabetic neuropathy, DM – Diabetes mellitus, BP – Blood pressure, HDL – High density lipoproteins, BMI – Body mass index |
|

**Structural changes***:* RNFL was significantly thinner (p=0.04), and RPE was significantly thicker (p=0.01) in subjects with DN when compared to those without DN. The central foveal thickness was also thicker with probability approaching significance (p=0.06).[Table 2]

**Visual functions assessment**: Table 2 gives the mean scores for the BCVA, contrast sensitivity, mean retinal sensitivity and colour vision. Visual functions were significantly worse in subjects with DN when compared to those who had no DN; visual acuity was significantly lower by 0.9 LogMAR units; contrast sensitivity significantly worse by 0.11 Log units; colour vision was significantly impaired and mean retinal sensitivity was significantly lower.

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| **Table 2: Ocular risk factors associated with diabetic neuropathy in subjects with no DR** |
| **Risk factors, Mean ± SD** | **NO DR** |  **Diabetic Neuropathy** | ***P*** |
|  |  **N** |  **Absent**  |  **Present**  |  |
| **Retinal thickness, µm** | **605** | **n(%) = 472 (78)** | **n(%) = 133 (22)**  |  |
| Central foveal thickness |  | 169.77±18.88 | 173.59 ±26.9 | 0.06 |
| Mean retinal thickness |  | 288. 51 ± 132.53 | 278.22 ± 99.0 | 0.45 |
| Photoreceptor layer |  | 63.48 ± 33.92 | 62.76 ± 7.2 | 0.81 |
| Retinal nerve fiber layer |  | 6.39 ± 5.57  | 5.33 ± 3.6 | 0.04\* |
| Retinal Pigment Epithelium |  | 68.53 ± 7.4 | 70.6 ± 8.2 | 0.01\* |
| **Visual Functions**  | **613** | **n (%) =485 (79.1)** | **n(%) =128 (20.9)** |  |
| Contrast sensitivity, log units |  | 1.36 ± 0.17 | 1.25 ± 0.21 | 0.0001\* |
|  | **245** | **n(%) = 208 (84.9)** |  **n(%) = 37 (15.1)** |  |
| Mean Retinal sensitivity, db |  | 14.78 ± 3.17 | 13.56 ± 3.65 | 0.03\* |
| Colour vision, total error scores |  | 189.63 ± 94.92 | 228.5 ± 117.5 | 0.04\* |
|  | **743** | **n(%) = 558 (75.1)**  | **n(%) = 185 (24.9)** |  |
| Visual acuity, logMAR |  | 4.8 ± 2.0 | 5.7 ± 2.4 |  0.0001\* |
| DR -Diabetic retinopathy, µm - Micrometers, db - decibel, n(%) - number (percentage), \* - p < 0.05 |
|

Table 3 shows unadjusted and adjusted odds ratios of the variables that were associated with the DN. After adjusting for variables including age, gender, duration of diabetes, Hba1c and systolic BP, the mean retinal sensitivity was significantly associated with the presence of DN (p= 0.01) [Table 3]. Figure 1 shows that the VPT and retinal sensitivity were inversely related (r = -0.16, R2 = 0.02, p = 0.01).

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| **Table 3: Risk factors associated with the presence of diabetic neuropathy**  |
|   |   |   |   |   |
| Variables |  Unadjusted |  Adjusted |
| Odds Ratio (95% CI)  | *p* | Odds Ratio (95% CI)  | *p* |
| Age, years | 1.08 (1.06 – 1.10) | 0.00001\* | 1.06 (0.98 – 1.15) | 0.13 |
| Duration of DM, years | 1.10 (1.06 – 1.13) | 0.0001\* | 1.1(0.98 – 1.23) | 0.08 |
| Systolic BP, mm Hg  | 1.01 (1.00 – 1.02) | 0.004\* | 0.98 (0.95 – 1.01) | 0.27 |
| Gender (male) | 0.81 (0.58 – 1.13) | 0.22 | 1.25 (0.36 – 4.32) | 0.72 |
| RNFL thickness, µm | 0.95 (0.90 - 0.99) | 0.04\* | 0.85 (0.70 - 1.0) | 0.12 |
| RPE thickness, µm | 1.03 (1.01 - 1.06) | 0.007\* | 0.96 (0.89 - 1.0) | 0.27 |
| Mean retinal sensitivity, dB | 0.89 (0.81-0.99) | 0.03\* | 0.81 (0.66 - 0.99) |  0.04**\*** |
| Colour vision, total error scores | 1.00 ( 1.00 - 1.00) | 0.02\* | 0.99 ( 0.98 - 1.0) | 0.84 |
| Contrast sensitivity, log units | 0.05 ( 0.02 - 0.15) | 0.0001\* | 0.23 ( 0.00 - 11.36) | 0.46 |
| Visual acuity, logMAR | 1.17(1.09 – 1.26)  | 0.0001\* | 0.56(0.23– 1.30) | 0.20 |
| \* - p < 0.05, DM – Diabetes Mellitus |

**DISCUSSION**

DR and its effect on various visual functions have been well described in the literature. Various retinal structural and visual function variables have been identified to serve as possible markers for early neuronal damage in the diabetic retina.[7-10] However, the clinical utility of these variables in predicting the presence of DN in absence of any DR has not been addressed fully in the literature. The present study explored whether subjects with DN also show structural and visual function changes in the retina with the assumption that structural and visual function parameters that have a neuropathic origin will serve as useful predictors for the detection of DN. Our results show that diabetic subjects with DN but no DR show an increase in the foveal thickness, reduced RNFL thickness and a significant reduction in visual functions such as visual acuity, contrast sensitivity, mean retinal sensitivity and colour vision, when compared to those without DN.

Our results showed a significant macular RNFL thinning of 1.06 microns in subjects with DN as compared to those without DN. Shahidi et al[12] had also reported a thinning of 1.5 microns of the RNFL layer around the optic disc in subjects with DN but no DR. The RNFL thinning is possibly attributed to the apoptosis of the retinal neural cells, and neuro-degeneration due to the influence of various factors such as oxidative stress, increased glucose flux and pro-inflammatory cytokines.[11]

Visual acuity has been shown to be affected in DR even in absence of macular ischemia, possibly due to altered central foveal thickness and changes in microcirculation.[17] Our data suggest that reduced visual acuity occurs in subjects with DN before any DR has set in. To our knowledge, reduced visual acuity in DN subjects without DR has not been reported earlier. Literature suggests that RNFL thinning is associated with DN and we postulate that a thinned out RNFL in diabetic eyes with DN decreases or delays the visual information to be carried to the lateral geniculate nucleus, thereby leading to reduced visual function. Our data also show that the presence of DN compared to those with no DN is significantly associated with increased duration of diabetes (p=0.0001), suggesting an increase in fibrosis and angiogenesis that may directly affect visual functions.[18]

A significant decrease in colour vision sensitivity was also shown in subjects with DN compared to those without DN. Various reasons for colour vision loss in diabetic eyes include metabolic derangement of the neural retina, hypoxia and oxidative stress.[19] Earlier studies have described colour vision deficits in subjects with and without DR, however, the association with established DN has been not shown to date.[20]

Contrast sensitivity is known to be affected in diabetics even in absence of DR.[21] Pre-diabetic hyper insulinemia and toxic inflammatory factors might affect the ganglion cell layer of the neural retina, resulting in reduced visual functions including contrast sensitivity.[22] Results from our study demonstrate that subjects with DN have reduced contrast sensitivity compared to those without DN. This is in agreement with Efron et al[11] who suggest that disrupted neural component (comprising ganglion cell layer, amacrine and bipolar cell layers),and neural damage associated with increased neural noise, results in compromised visual acuity and contrast sensitivity in DN.

Our study is the first to demonstrate that the presence of DN but no DR significantly reduces the retinal sensitivity. Possible reasons for this include optical degradation effects due to increased retinal thickness and early damage in the inner retinal layers.[23,24] Also, previous data from our own group suggest that central foveal thickness is significantly associated with the abnormal retinal sensitivity in diabetic subjects who had no DR.[25] Retinal sensitivity changes in our subjects with DN but no DR support the theory that neuronal changes occur before the onset of vascular dysfunction. To date, corneal and RNFL have been advocated as potential bio-markers of early peripheral DN.[11] Based on the data of this study, we suggest that retinal sensitivity could also be a possible retinal marker for DN.

The major finding of our study indicates that diabetic subjects who have DN but no DR show early neurological alterations, evidenced by reduced retinal sensitivity. Although loss of visual sensitivity in subjects with DN has been reported by Sampson et al[13], the current study differs from the referred in various methodological aspects: the earlier hospital based study was conducted on a relatively small sample (n=70) whereas ours is a population-based study with large sample size (n=743). In addition, the study by Sampson et al., they included subjects who had mild DR whilst our study did not include any subjects who had DR. Sampson et al.’s study also showed no difference in visual sensitivity between subjects with and without DN in the central visual field. They reported that the difference increased in peripheral visual fields. On the other hand, we only examined subjects with no DR and showed that subjects with DN (and no DR) had lower central field sensitivity compared to those who had no DN and DR. In addition, the visual sensitivity in their study was assessed using routine clinical standard perimetry whilst we used microperimetry which is a more central field test with additional features of fixation stability tracking and visual fields mapping to the retinal area, which makes it more sensitive over the standard perimetry.

A recent review by de Moraes et al[26] has highlighted other visual function parameters, such as oscillatory potentials and delays in b-wave latency, can also predict DN. It would have been important to examine how the subjects from our own study progressed with their DR status over time. However, as the follow up study was not carried out it is difficult to comment on this. A future longitudinal study could be designed to explore the distinct mechanisms of retinal neuronal changes, peripheral DN and DR and to ascertain whether the onset of DR could be predicted by retinal sensitivity changes in subjects with DN.

A possible limitation of this study is the use of biothesiometer probe to measure vibration perception thresholds for peripheral DN. However, it would be difficult to use alternative methods like nerve conduction studies and neuropathy symptom score estimations in an epidemiological study like ours.

Further studies involving mfERG for early detection of neuro-retinal dysfunction and OCT angiography to identify early capillary dropouts may help in understanding the causations and associations of early ocular (neural and vascular) changes in subjects with peripheral DN.

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**Contributors:**

Designed the study: TS, RR

Data acquisition: LG, SSP, SG, TS, RR

Statistical analysis plan: SN, SP, LG, RR

Analysed the data and data interpretation: SN, SP

Drafting and revising the manuscript: SN, SP, RR

Final approval: SP, LG, SSP, SG, TS, RR

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**Figure Legends:**

**Figure 1**

Scatter plot representing a negative correlation between the mean retinal sensitivity and vibration perception thresholds in retinopathy absent diabetics. Solid line indicates the line of best fit, dashed lines indicates the upper and lower limits of 95 % CI.